

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 511 917 B1

(12)

FASCICULE DE BREVET EUROPEEN

(45) Date de publication et mention
de la délivrance du brevet:
23.10.1996 Bulletin 1996/43

(51) Int Cl.⁶: C07H 15/252, C07F 7/18,
C07H 15/203, A61K 31/70,
C07H 15/26

(21) Numéro de dépôt: 92401218.0

(22) Date de dépôt: 29.04.1992

(54) Prodrogues glycosylées, leur procédé de préparation et leurs utilisations

Glykosylierte Arzneimittel-Vorstufen, Verfahren zu ihrer Herstellung und ihre Verwendungen

Glycosylated prodrugs, process for their preparation and uses thereof

(84) Etats contractants désignés:
AT BE CH DE DK ES FR GB GR IT LI LU NL PT SE

(30) Priorité: 30.04.1991 FR 9105326

(43) Date de publication de la demande:
04.11.1992 Bulletin 1992/45

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(56) Documents cités
EP-A- 0 410 366

EP 0 511 917 B1

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produkt 4-Nitrophenyl-2-(2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl)-5-nitrobenzylcarbonat der Formel 47 einsetzt

72. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-2-((2,3,4-tri-O-acetyl- β -D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 53 einsetzt.

73. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-4-methoxy-5-nitro-2-((2,3,4-tri-O-acetyl- β -D-glucopyranosyl)methyluronat)benzylcarbonat der Formel 67 einsetzt.

74. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Nitrophenyl-4-(2,3,4-tri-O-acetyl- β -D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 69 einsetzt.

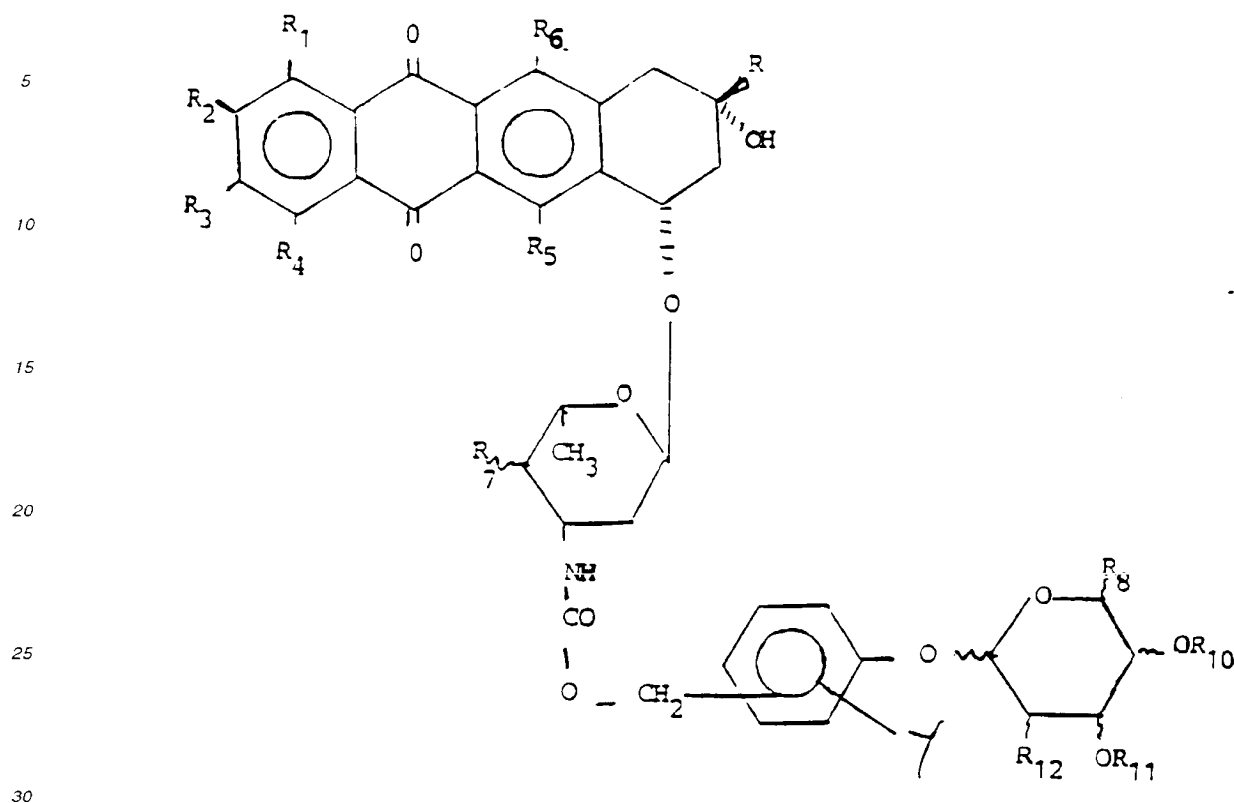
75. Verfahren zur Herstellung nach einem der Ansprüche 1 bis 27, dadurch **gekennzeichnet**, daß man als Zwischenprodukt 4-Chlorphenyl-2-((2,3,4-tri-O-acetyl- β -D-glucopyranosyl)methyluronat)-5-nitrobenzylcarbonat der Formel 81 einsetzt.

76. Verfahren zur Herstellung eines Arzneimittels zur Behandlung von Krankheiten, an denen aktivierte Makrophagen, aktivierte Granulozyten, aktivierte Thrombozyten oder aktivierte Tumorzellen beteiligt sind, dadurch **gekennzeichnet**, daß man eine Arzneimittelvorstufe nach einem der Ansprüche 1 bis 27 einsetzt.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. An anthracycline prodrug, characterized in that it has formula I below:



in which

R_1 , R_2 and R_3 , which can be identical or different, are a hydrogen atom or a hydroxyl group;
 R_4 is a hydrogen atom, a hydroxyl group or a methoxy group;
 R is a group $\text{CO}-\text{CH}_2-\text{R}''$, in which R'' is a hydrogen atom, a C_1 - C_6 alkyl group, a hydroxyl group, an alkoxy group, an O-acyl group or an aryl group;
 R_5 and R_6 , which can be identical or different, are a hydrogen atom or a hydroxyl group;
 R_7 is a hydrogen atom or a hydroxyl group;
 R_8 is a group $-\text{CH}_2-\text{OR}_9$ or a group COOR_9 , where R_9 is a C_1 - C_3 alkyl or a hydrogen atom;
 R_{10} and R_{11} are a hydrogen atom, an acyl protecting group or an alkyl group;
 R_{12} is a hydroxyl group, an amine group, an amide group or an O-acyl protecting group;
the benzyl $-\text{CH}_2$ is preferably in the para or ortho position to the glycosyl oxygen; and
 Y is a hydrogen atom, or at least one electron-attracting group selected especially from the group comprising the NO_2 group, a halogen atom and a group SO_2X (where $\text{X} = -\text{CH}_3$, $\text{C}_6\text{H}_4-\text{CH}_3$, NH_2 , $\text{N}-(\text{C}_1-\text{C}_4 \text{ alkyl})_2$ or $\text{NH}-\text{C}_1-\text{C}_4 \text{ alkyl}$), $-\text{CN}$, acyl or COO-alkyl , and/or at least one electron-donating group selected from the group comprising groups of the type O-alkyl, NHCO-alkyl , N(alkyl)CO-alkyl , S-alkyl or alkyl.

2. A prodrug according to Claim 1, characterized in that when Y is one or more electron-attracting groups, these are preferably in the ortho and/or para position to the glycosyl oxygen, and when Y is one or more electron-donating groups, these are preferably in the meta position.
3. A prodrug according to Claim 1 or Claim 2, characterized in that the preferred compounds of formula I contain the

R_5 and R_6 are hydroxyl groups,

R is a $-\text{CO}-\text{CH}_3$ group or a $-\text{CO}-\text{CH}_2\text{OH}$ group,

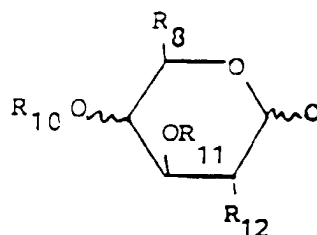
R_7 is a hydrogen atom or a hydroxyl group,

R_8 is a $-\text{CH}_2-\text{OAc}$, $-\text{CH}_2\text{OH}$, $-\text{COOMe}$ or $-\text{COOH}$ group,

R_{10} and R_{11} , which can be identical or different, are a hydrogen atom or an Ac group,

R_{12} is a hydroxyl group or an OAc group,

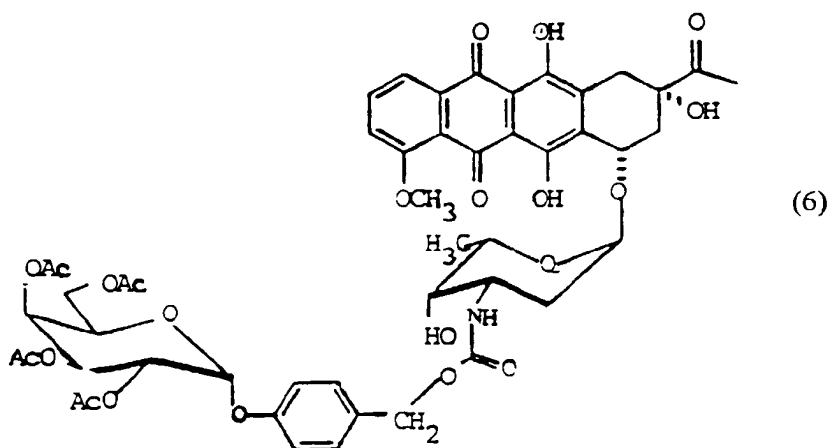
said radicals R_8 , R_{10} , R_{11} and R_{12} preferably being in the following positions:



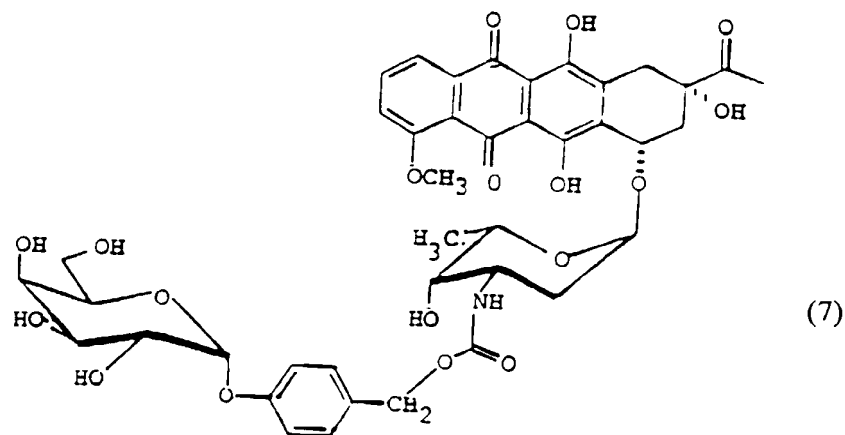
and

Y is a hydrogen atom, an NO_2 group or a chlorine atom in the para or ortho position to the glycosyl oxygen, and/or an OCH_3 group in the meta position to the glycosyl oxygen.

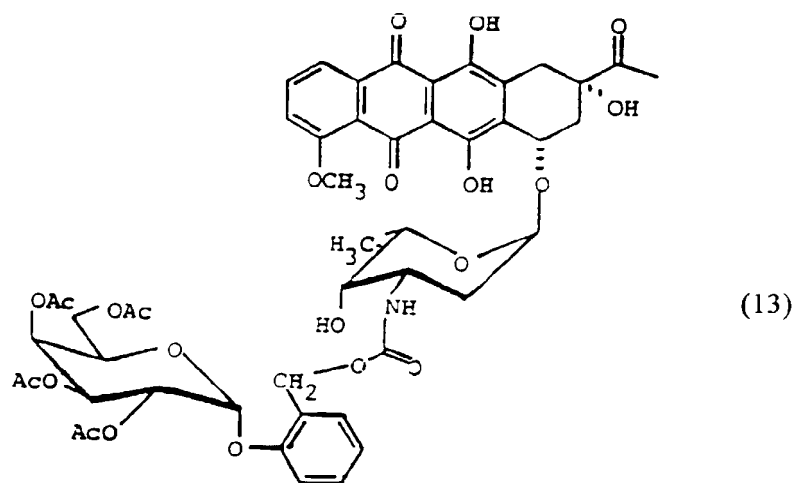
4. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 6 below:



5. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 7 below:

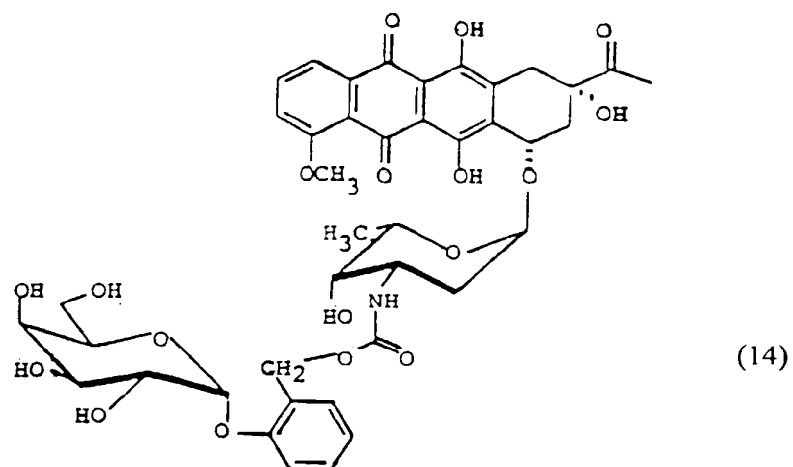


20 6. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 13 below:

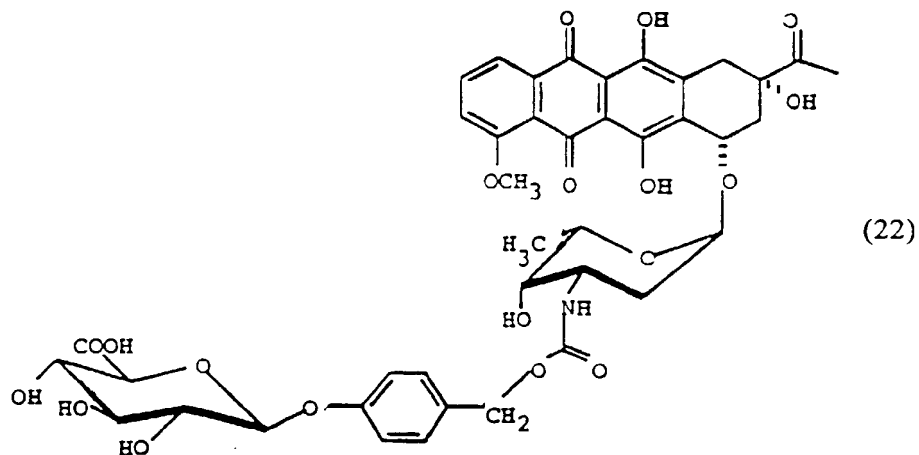


45 7. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 14 below:

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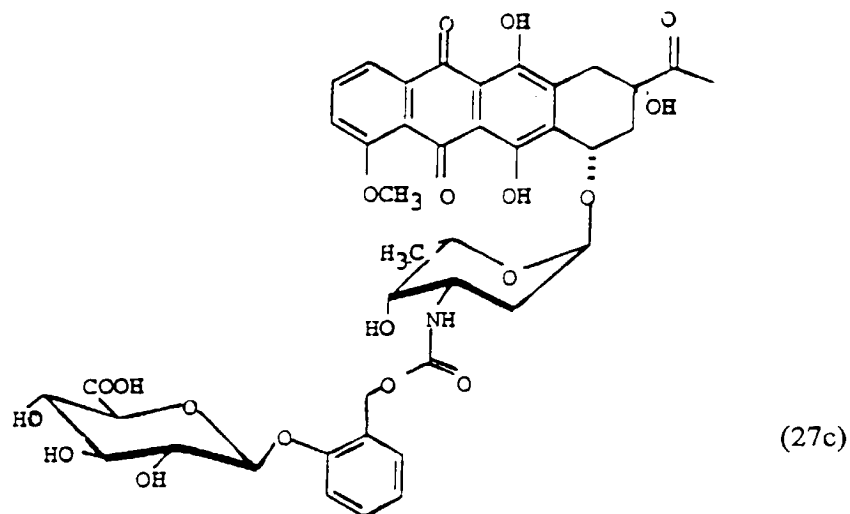


20 8. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 22 below:

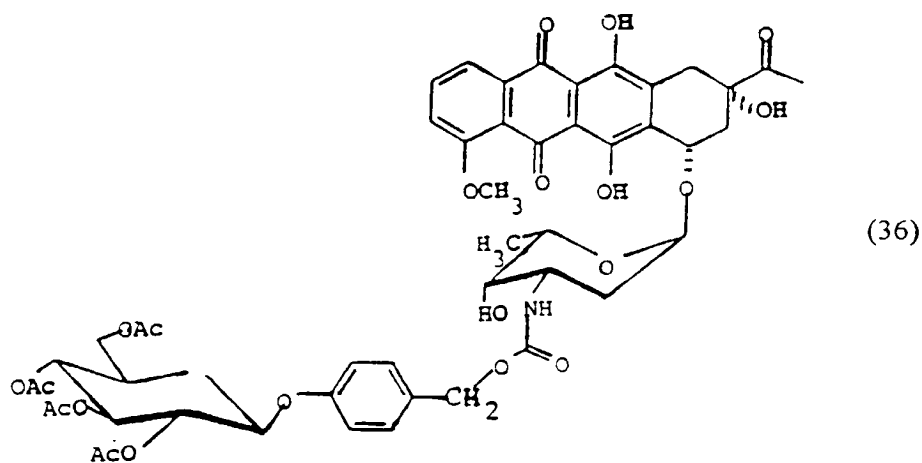


45 9. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 27c below:

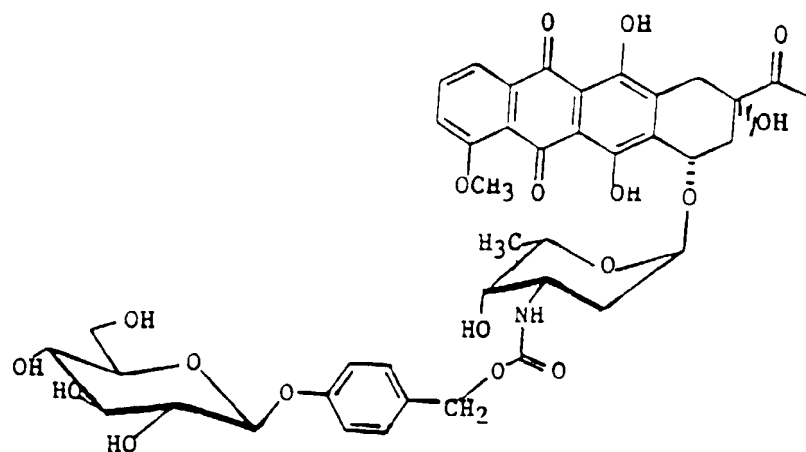
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25 10. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 36 below:

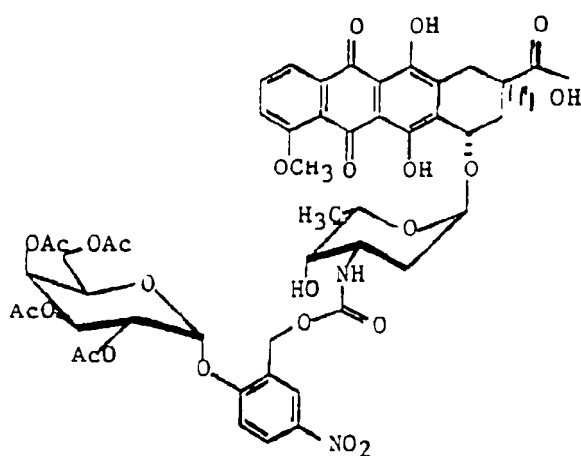


50 11. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 37 below:



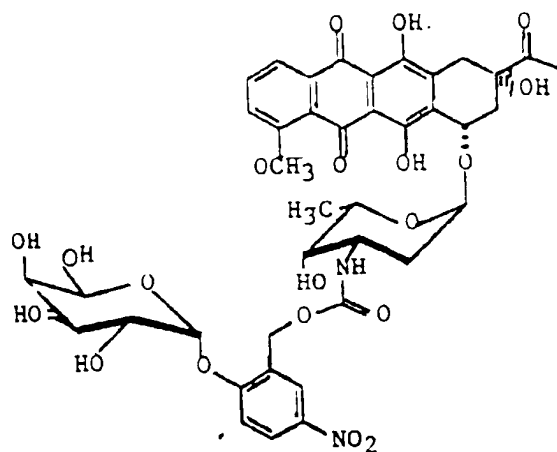
(37)

12. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 48a below:



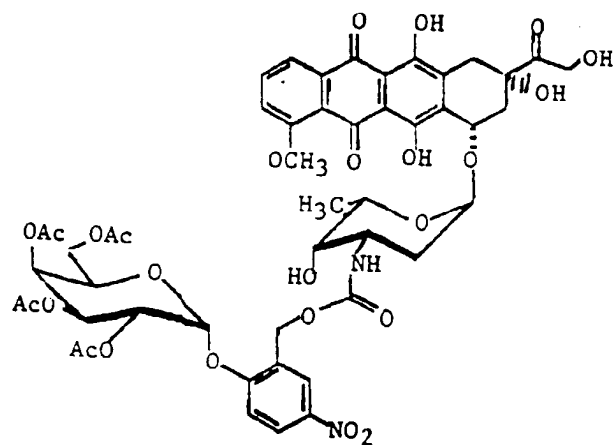
(48a)

13. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 48b below:



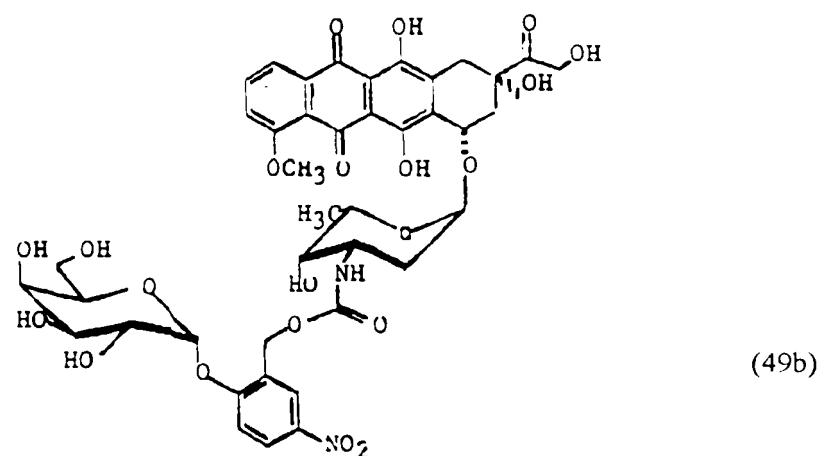
(48b)

14. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 49a below:

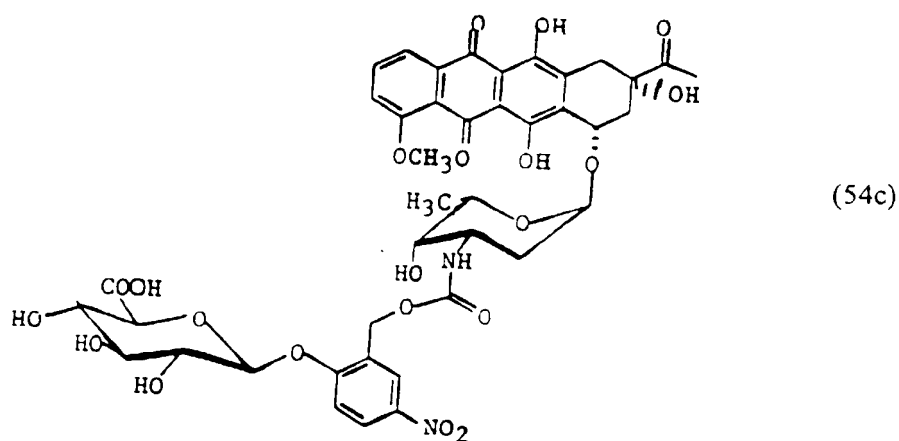


(49a)

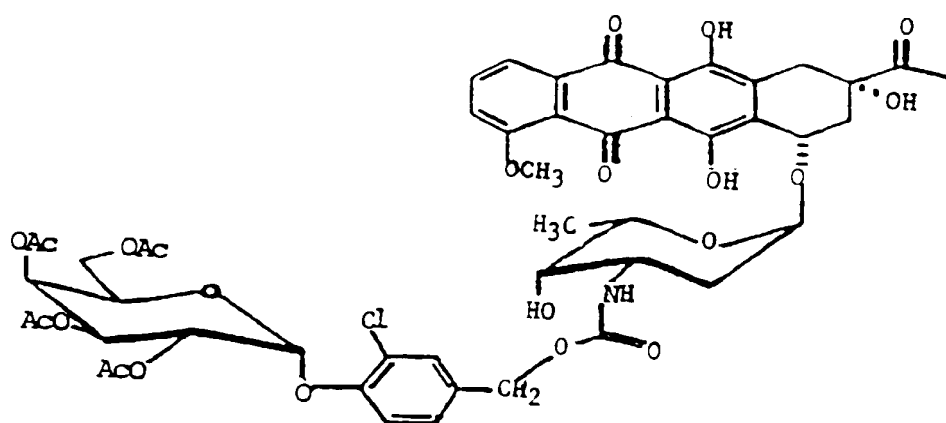
15. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 49b below:



16. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 54c below:

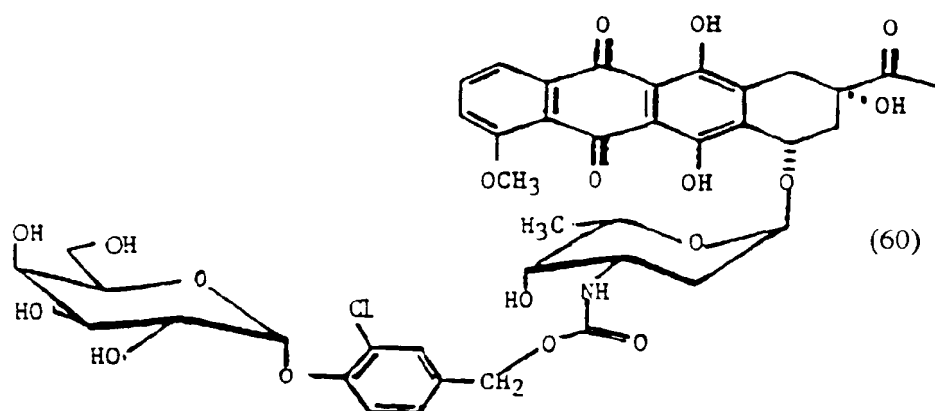


17. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 59 below:



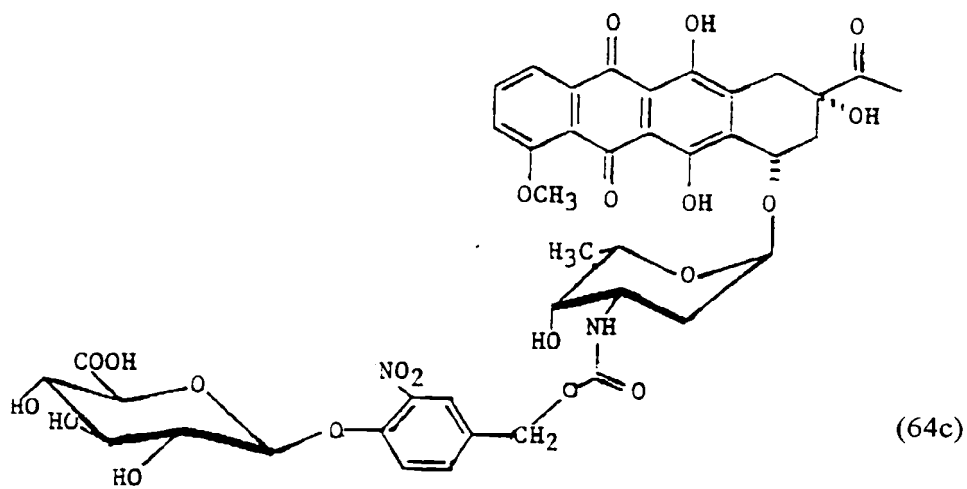
(59)

18. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 60 below:

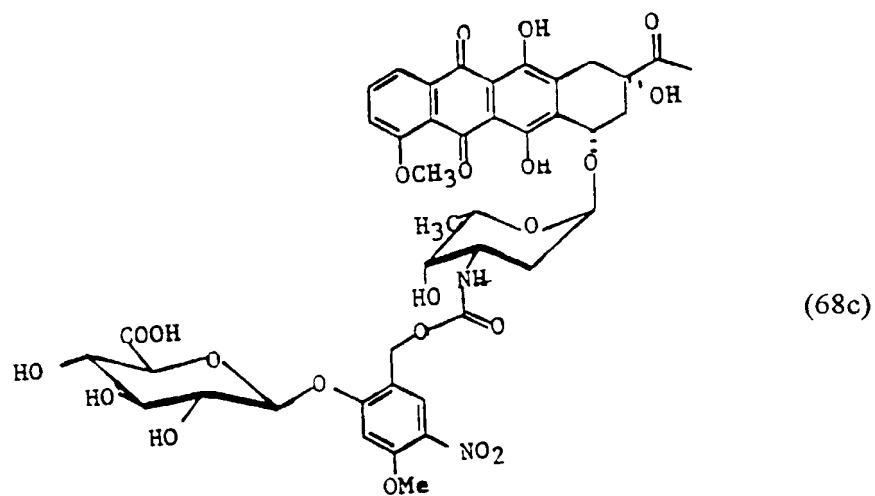


(60)

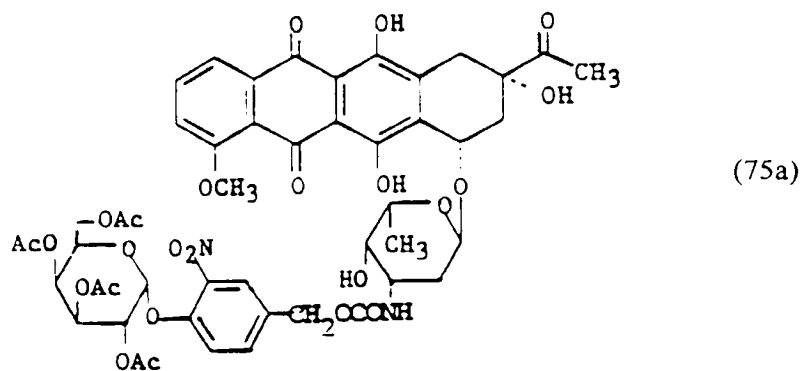
19. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 64c:



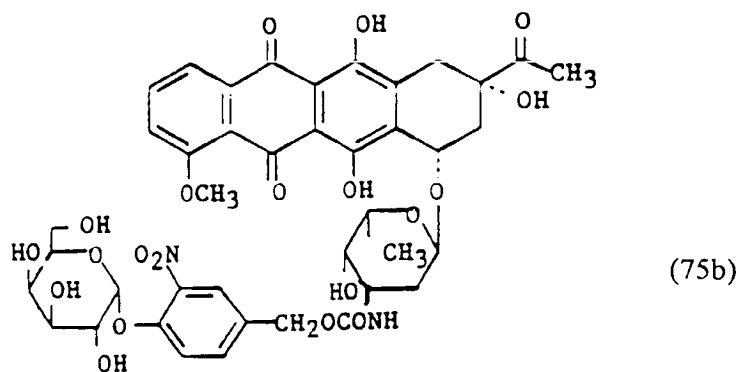
25 20. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 68c below:



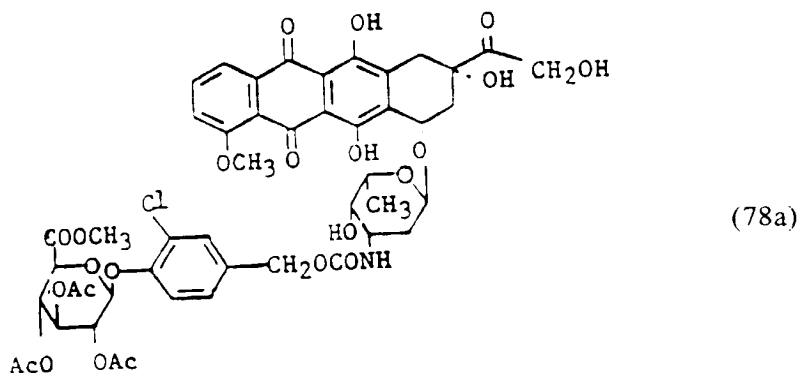
50 21. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 75a below:

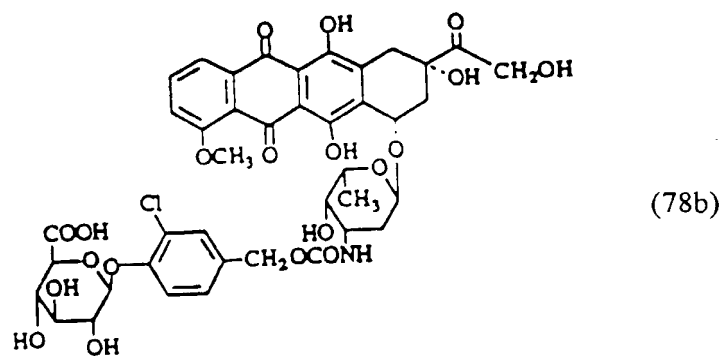


22. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 75b below:

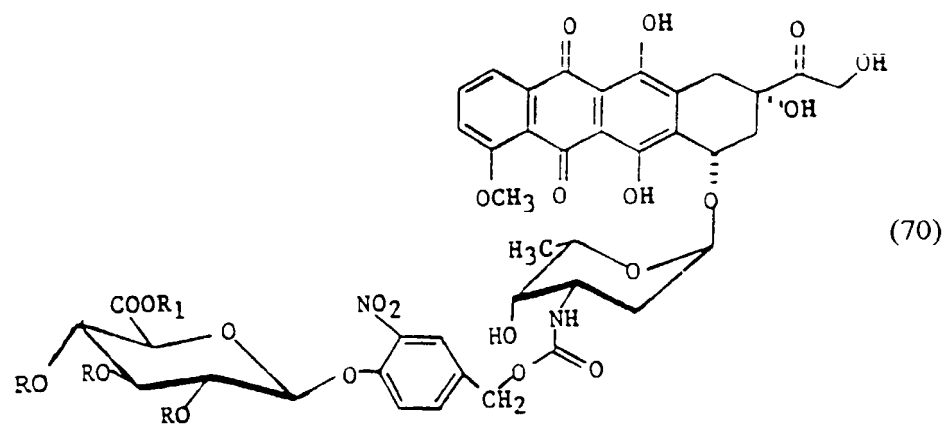


23. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 78a below:





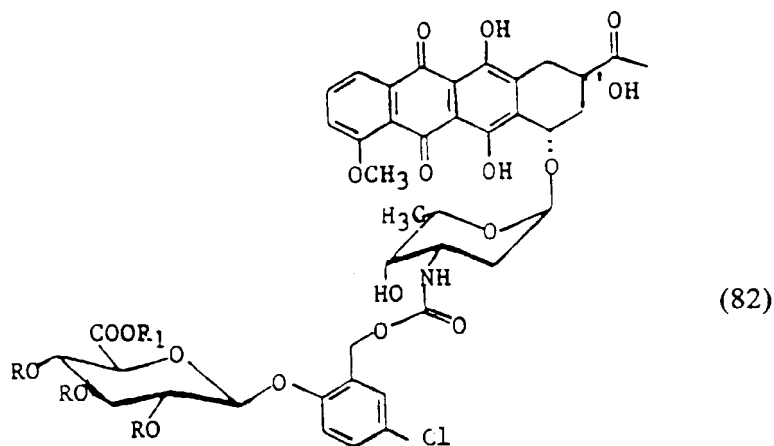
25. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 70c below:



with:

- 70a: R=Ac R₁=CH₃
- 70b: R=H R₁=CH₃
- 70c: R=R₁=H

26. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 82 below:



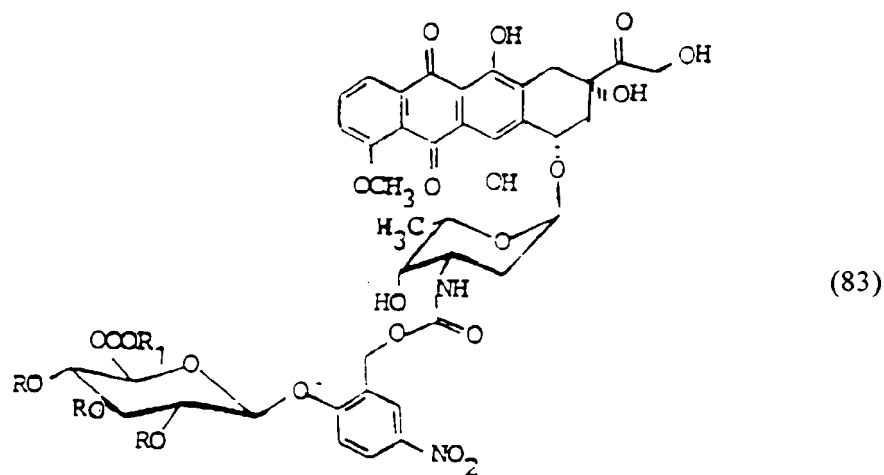
with:

82a : R=Ac, R₁=CH₃

82b : R=H, R₁=CH₃

82c : R=R₁=H

27. A prodrug according to any one of Claims 1 to 3, characterized in that it has formula 83 below:



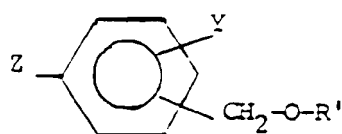
with:

83a : R=Ac, R₁=CH₃

83b : R=H, R₁=CH₃

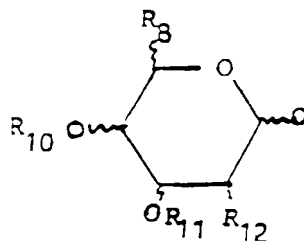
83c : R=R₁=H

28. A method of preparing a compound of formula I, which in particular can be degraded by a glycosidase, characterized in that it comprises

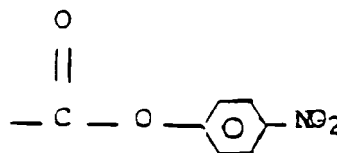
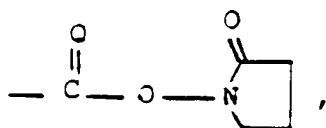


(A)

in which
Z is a hydroxyl group, an O-trialkylsilyl group or a group

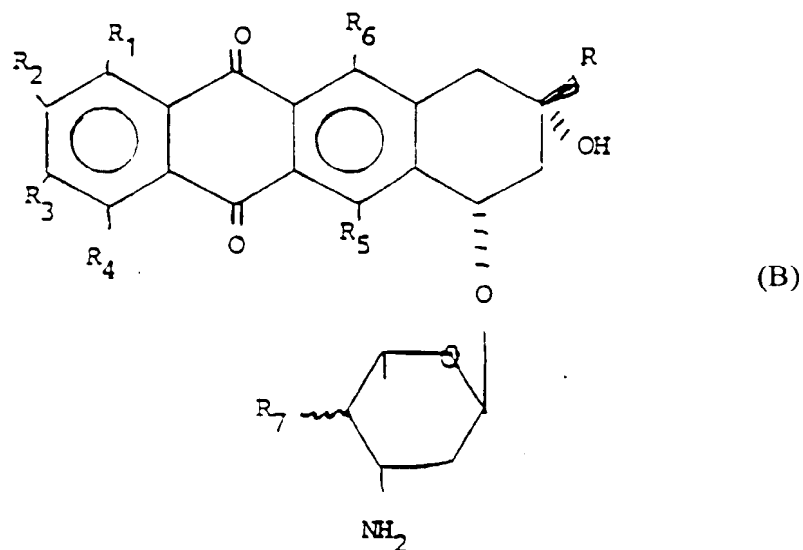


in which R₈, R₁₀, R₁₁ and R₁₂ are as defined above;
R' is one of the following groups:



the benzyl -CH₂ is preferably in the para or ortho position to the phenol group, which may be modified (glycosylated or silylated); and

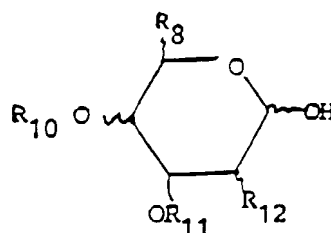
Y is a hydrogen atom, or at least one electron-attracting group selected especially from the group comprising the NO₂ group, a halogen atom and a group SO₂X (where X = -CH₃, C₆H₄-CH₃, NH₂, N-(C₁-C₄ alkyl)₂ or NH-C₁-C₄alkyl), -CN, acyl or COO-alkyl, and/or at least one electron-donating group selected from the group comprising groups of the type O-alkyl, NH-CO-alkyl, N(alkyl)CO-alkyl, S-alkyl or alkyl, with an anthracycline of formula B:



25 in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R are as defined above;

(2) the removal of the protecting groups present in the compounds obtained, especially by hydrolysis, transesterification or saponification; and

(3) if appropriate, suitable condensation with an ose of the following formula:



40 in the case where Z is a hydroxyl group or an O-tri-alkylsilyl group, to give an anthracycline prodrug of formula I, in which all the radicals R_1 to R_{12} and R are as defined above.

29. A method according to Claim 28, characterized in that, prior to step (1), the glycosylated p-hydroxybenzyl derivative is obtained by:

- 45
- (a) fusion of a cresol with an ose or a peracetylated methyl glucuronate;
 - (b) benzyl bromination of the product obtained;
 - (c) solvolysis of the brominated derivative, and
 - (d) activation of the hydroxyl group with a hydroxysuccinimidyl or paranitrophenoxycarbonyl derivative

50 30. Products comprising a modified anthracycline prodrug according to any one of Claims 1 to 27, and an enzyme/tumour-specific antibody conjugate of formula II:

Ab-Sp-E

(II)

biomolecule which tends to accumulate in a tumour, such as EGF (epidermal growth factor), α -TGF (α transforming growth factor), PDGF (platelet derived growth factor), IGF I+II (insulin growth factor I+II) or FGF a+b (fibroblast growth factor a+b),

E is a glycosidase which is not immunogenic or has a very low immunogenicity, preferably a mammalian glycosidase such as α - or β -glucosidase, α -galactosidase, α - or β -mannosidase, α -fucosidase, N-acetyl- α -galactosaminidase, N-acetyl- β -N-acetyl- α -glucosaminidase or β -glucuronidase, and

Sp (arm) is a group containing a sulphide or a disulphide, of formula III or IV:



or a polypeptide arm, in which

X' or Y' is -CO-R₁₃-(N-succinimido)- or -C(=R₁₄)-CH₂-CH₂-, where R₁₃ is a -CH₂-CH₂, 1,4-cyclohexylidene, 1,3- or 1,4-phenylene or methoxycarbonyl- or chloro- 1,4-phenylene group and R₁₄ is an oxygen atom or an NH group,

Y' represents -C(=R₁₄)-CH₂-CH₂ when R₁₄ is as defined above, and
n is 1 or 2,

for use in cytostatic therapy, either simultaneously, separately or spread out over a period of time.

31. 4-Bromomethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 2, an intermediate in the method according to Claim 28.
32. 4-Formylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 3, an intermediate in the method according to Claim 28.
33. 4-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 4, an intermediate in the method according to Claim 28.
34. 2-Bromomethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 9, an intermediate in the method according to Claim 28.
35. 2-Formylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 10, an intermediate in the method according to Claim 28.
36. 2-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 11, an intermediate in the method according to Claim 28.
37. Methyl (4-bromomethylphenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 16, an intermediate in the method according to Claim 28.
38. Methyl (4-formylphenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 17, an intermediate in the method according to Claim 28.
39. Methyl (4-hydroxymethylphenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 18, an intermediate in the method according to Claim 28.
40. Methyl (2-bromomethylphenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 23, an intermediate in the method according to Claim 28.
41. Methyl (2-hydroxymethylphenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 24, an intermediate in

od according to Claim 28

43. 2-Tert-butylidimethylsilyloxybenzaldehyde of formula 28, an intermediate in the method according to Claim 28.
- 5 44. 2-Tert-butylidimethylsilyloxybenzyl alcohol of formula 29, an intermediate in the method according to Claim 28.
45. N-[2-Hydroxybenzyloxycarbonyl]daunorubicin of formula 32, an intermediate in the method according to Claim 28.
- 10 46. 4-Formylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside of formula 33, an intermediate in the method according to Claim 28.
47. 4-Hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside of formula 34, an intermediate in the method according to Claim 28.
- 15 48. N-[4-Hydroxybenzyloxycarbonyl]daunorubicin of formula 38, an intermediate in the method according to Claim 28.
49. 2-Methyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 42, an intermediate in the method according to Claim 28.
- 20 50. 2-Bromomethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 43, an intermediate in the method according to Claim 28.
51. 2-Dibromomethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 44, an intermediate in the method according to Claim 28.
- 25 52. 2-Formyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 45, an intermediate in the method according to Claim 28.
53. 2-Hydroxymethyl-4-nitrophenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 46, an intermediate in the method according to Claim 28.
- 30 54. Methyl (2-formyl-4-nitrophenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 51, an intermediate in the method according to Claim 28.
- 35 55. Methyl (2-hydroxymethyl-4-nitrophenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 52, an intermediate in the method according to Claim 28.
56. 2-Chloro-4-methylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 55, an intermediate in the method according to Claim 28.
- 40 57. 2-Chloro-4-bromomethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 56, an intermediate in the method according to Claim 28.
58. 2-Chloro-4-hydroxymethylphenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 57, an intermediate in the method according to Claim 28.
- 45 59. Methyl (4-formyl-2-nitrophenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 61, an intermediate in the method according to Claim 28.
- 50 60. Methyl (4-hydroxymethyl-2-nitrophenyl 2,3,4-tri-O-acetyl- β -D-glucopyranoside)uronate of formula 62, an intermediate in the method according to Claim 28.
61. (4-bromomethyl 2-nitro)-phenyl 2,3,4,6-tetra-O-acetyl- α -D-galactopyranoside of formula 73, an intermediate in the method according to claim 28.

63. 4-hydroxy-3-chlorobenzaldehyde 2,3,4-tri-O-acetyl- β -D-methylglucuronide of formula 76, an intermediate in the method according to claim 28.
- 5 64. (4-hydroxy-methyl-2-chloro)-phenyl 2,3,4-tri-O-acetyl- β -D-methylglucuronide of formula 77, an intermediate in the method according to claim 28.
65. 2,5-Dioxopyrrolidin-1-yl 4-(2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl)benzyl carbonate of formula 5, an intermediate in the method according to Claim 28.
- 10 66. 2,5-Dioxopyrrolidin-1-yl 2-(2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl)benzyl carbonate of formula 12, an intermediate in the method according to Claim 28.
67. 2,5-Dioxopyrrolidin-1-yl 4-(methyl (2,3,4-tri-O-acetyl- β -D-glucopyranosyl)uronate)benzyl carbonate of formula 19, an intermediate in the method according to Claim 28.
- 15 68. 4-Nitrophenyl 2-(methyl (2,3,4-tri-O-acetyl- β -D-glucopyranosyl)uronate)benzyl carbonate of formula 26, an intermediate in the method according to Claim 28.
69. 4-Nitrophenyl 2-(tert-butyldimethylsilyloxy)benzyl carbonate of formula 30, an intermediate in the method according to Claim 28.
- 20 70. 2,5-Dioxopyrrolidin-1-yl 4-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)benzyl carbonate of formula 35, an intermediate in the method according to Claim 28.
- 25 71. 2,5-Dioxopyrrolidin-1-yl 4-dimethyl-t-hexylsilyloxybenzyl carbonate of formula 40, an intermediate in the method according to Claim 28.
72. 4-Nitrophenyl 2-(2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl)-5-nitrobenzyl carbonate of formula 47, an intermediate in the method according to Claim 28.
- 30 73. 4-Nitrophenyl 2-(methyl (2,3,4-tri-O-acetyl- β -D-glucopyranosyl)uronate)-5-nitrobenzyl carbonate of formula 53, an intermediate in the method according to Claim 28.
- 35 74. 4-Nitrophenyl 4-methoxy-5-nitro-2-(methyl (2,3,4-tri-O-acetyl- β -D-glucopyranosyl)uronate)benzyl carbonate of formula 67, an intermediate in the method according to Claim 28.
75. 4-Nitro-phenyl 4-(methyl (2,3,4-tri-O-acetyl- β -glucopyranosyl)uronate)-5-nitro-benzyl carbonate of formula 69, an intermediate in the method according to claim 28.
- 40 76. 4-chlorophenyl 2-(methyl (2,3,4-tri-O-acetyl- β -D-glucopyranosyl)uronate)-5-nitrobenzyl carbonate of formula 81, an intermediate in the method according to claim 28.
77. Application of the prodrugs according to claims 1 to 27 to the preparation of drugs for the treatment of diseases, which involve activated macrophages, granulocytes, thrombocytes or human tumoural cells.
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Claims for the following Contracting States : ES, GR

1. A method of preparing anthracycline prodrugs having the following formula I:
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